JACC: CARDIOVASCULAR INTERVENTIONS

VOL. 7, NO. 11, 2014

ISSN 1936-8798/$36.00

PUBLISHED BY ELSEVIER INC.

http://dx.doi.org/10.1016/j.jcin.2014.06.010

PERIPHERAL VASCULAR

Pressure-Wire-Guided Percutaneous Transluminal Pulmonary Angioplasty

A Breakthrough in Catheter-Interventional Therapy for Chronic Thromboembolic Pulmonary Hypertension

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ABSTRACT

OBJECTIVES This study sought to prove the safety and effectiveness of pressure-wire-guided percutaneous transluminal pulmonary angioplasty (PTPA).

BACKGROUND PTPA has been demonstrated to be effective for treatment of chronic thromboembolic pulmonary hypertension. However, a major and occasionally fatal complication after PTPA is reperfusion pulmonary edema. To avoid this, we developed the PEPSI (Pulmonary Edema Predictive Scoring Index). The pressure wire has been used to detect insufficiency of flow in a vessel.

METHODS We included 350 consecutive PTPA sessions in 103 patients with chronic thromboembolic pulmonary hypertension from January 1, 2009 to December 31, 2013. During these 5 years, 140 PTPA sessions were performed without guidance, 65 with guidance of PEPSI alone, and 145 with both PEPSI and pressure-wire guidance. Each PTPA session was finished after achieving PEPSI scores of <35.4 with PEPSI guidance and each target lesion achieving distal mean pulmonary arterial pressure <35 mm Hg with pressure-wire guidance.

RESULTS The occurrence of clinically critical reperfusion pulmonary edema and vessel injuries were lowest in the group using the guidance of both pressure wire and PEPSI (0% and 6.9%, respectively). Furthermore, the group guided by pressure wire and PEPSI accomplished the same hemodynamic improvements with fewer numbers of target lesions treated and sessions performed.

CONCLUSIONS The combined approach using pressure wire and PEPSI produced more efficient clinical results and greatly reduced reperfusion pulmonary edema and vessel complications. This is further evidence that PTPA is an alternative strategy for treating chronic thromboembolic pulmonary hypertension. (J Am Coll Cardiol Intv 2014;7:1297–306) © 2014 by the American College of Cardiology Foundation.

Percutaneous transluminal pulmonary angioplasty (PTPA), or so-called balloon pulmonary angioplasty, has attracted attention as a new therapy for patients with chronic thromboembolic pulmonary hypertension (CTEPH) because of its effectiveness in alleviating symptoms and improving pulmonary circulation (1–11). However, the most crucial concern is that PTPA can induce reperfusion pulmonary edema (RPE) as a post-interventional complication, which sometimes leads to grave morbidity

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Manuscript received February 17, 2014; revised manuscript received May 24, 2014, accepted June 8, 2014.

ABBREVIATIONS AND ACRONYMS

6MWD = six-minute-walk distance

BNP = B-type natriuretic peptide

CTEPH = chronic thromboembolic pulmonary hypertension

IQR = interquartile range

PAP = pulmonary arterial pressure

PEPSI = Pulmonary Edema Predictive Scoring Index

PTPA = percutaneous transluminal pulmonary angioplasty

PVR = pulmonary vascular resistance

RPE = reperfusion pulmonary edema

and mortality (1–3). That is the main reason this less invasive, useful strategy has not progressed and has been suspended for a long time.

In 2001, Feinstein et al. (1) first reported the results of pulmonary balloon angioplasty in a collective group of patients, in which he showed that 11 of 18 patients (61%) developed RPE after balloon pulmonary angioplasty. In our previous report, based on our initial experiences, 27 of 51 cases (53%) developed RPE, and the patients with more severe clinical signs and/or hemodynamic abnormalities at baseline had a higher risk of RPE (2). Importantly, we recently demonstrated the usefulness of the PEPSI (Pulmonary Edema Predictive Scoring Index) as a promising predictor to avoid significant RPE (3). If the endpoint per each PTPA session were determined with PEPSI scores of <35.4, the negative predictive value of RPE would be 92.3% (3). However, PEPSI is calculated by pulmonary flow grade scoring (grades 0, 1, 2, and 3), the determination of which needs subjective judgment based on pulmonary arterial and venous flows (3). Therefore, an additional new objective tool to avoid significant RPE has long been desired.

The mean pulmonary arterial pressure (PAP) is normally <25 mm Hg. It has been reported that development of RPE correlates with mean PAP >35 mm Hg before angioplasty (1). In our experience, the median value of mean PAP before angioplasty in cases without RPE was 33 mm Hg (3). These findings suggest that if the pulmonary peripheral arteries are suddenly exposed to pressure >33 mm Hg, RPE would ensue through their capillary permeability. Therefore, we hypothesized that if the pressure level of the vasculatures distal to the target lesions after angioplasty can be measured accurately, and if its level can be regulated <35 mm Hg, then PTPA will be performed safely without risk of RPE. To clarify this hypothesis, we have begun using a pressure-wire-guided technique. The pressure wire can measure the proximal and distal pressures across the target lesions in addition to serving as a guidewire to insert balloon catheters. Furthermore, if the PTPA procedures are performed under guidance of a pressure wire, vessel injuries due to overdilation by balloon catheters or wire perforations will be reduced, leading to safer PTPA procedures.

Therefore, the purposes of this study were as follow: 1) to clarify the efficacy in hemodynamic improvement; and 2) to evaluate the prevalence of the complications, including RPE and vessel injuries, in our recent procedures, in which both the PEPSI and pressure-wire-guided techniques have been used, in comparison with those in our initial procedures without those techniques. If these approaches prove to be effective, they will contribute significantly to efficient and safe performance of PTPA even in less-experienced institutions all over the world.

METHODS

STUDY DESIGN. From January 2009 to December 2013, 350 consecutive PTPA sessions were performed on the 103 patients with CTEPH who were enrolled at Keio University Hospital or Kyorin University Hospital in Japan. The patients were diagnosed with CTEPH by demonstration of organized pulmonary thromboembolism using contrast-enhanced lung computed tomography, perfusion lung scintigraphy, and pulmonary angiography and ruling out collagen vascular disease, pulmonary disease, left heart abnormality, and other systemic diseases by blood tests, pulmonary function tests, and echocardiography. All patients provided written informed consent, and the performance of PTPA and analysis of clinical data in the present study were approved by the institutional review boards of Kyorin University Hospital and Keio University Hospital. Some of the enrolled patients and a portion of the data used for analysis in this study are the same as in our previous reports (2–6).

EXAMINATIONS. Patients underwent right-sided heart catheterization just before and after PTPA and at the follow-up examinations. Follow-up right-sided heart catheterization after the last procedure was performed at 3 to 6 months and at 12 months, and every year thereafter. Right atrial pressure, PAP, and pulmonary arterial wedge pressure were measured at the right-sided heart catheterization. Cardiac output was determined by the Fick technique using assumed oxygen consumption. Cardiac index was calculated by dividing cardiac output by body surface area. Pulmonary vascular resistance (PVR) was calculated by subtracting the pulmonary arterial wedge pressure from the mean PAP and dividing by cardiac output. Six-minute-walk distance (6MWD) and plasma B-type natriuretic peptide (BNP) level were determined both before PTPA and at the follow-up with the hemodynamics.

INDICATIONS FOR PTPA. The indications of PTPA (all items fulfilled) are the following: 1) mean PAP >30 mm Hg and PVR >3.75 Wood units (300 dyne/s/cm^{-5}), 2) New York Heart Association functional class >2; and 3) understanding of the interventional procedures and possible complications

and voluntary submission of informed consent. In June 2012, the indication was changed concerning the hemodynamic criteria: mean PAP >25 mm Hg if the lesions are angiographically accessible, because most patients with mean PAP >25 mm Hg are in New York Heart Association functional class II and the safety and effectiveness of PTPA are confirmed based on our initial experience.

Exclusion criteria for PTPA were serious comorbidity such as active infectious disease, severe chronic obstructive pulmonary disease, advanced hepatic disease, severe kidney disease, hemorrhagic tendency, poorly controlled diabetes mellitus, or uncontrolled hypertension. Patients who were unable to lie on the treatment table during the procedure were also excluded from the PTPA.

PROCEDURE OF PTPA. Coumadin was stopped for 3 days before the procedure and replaced by heparin, which was controlled to keep activated partial thromboplastin time within 60 to 80 s at the ward and active clotting time within 250 to 300 s during the procedure. Coumadin was restarted after PTPA and adjusted within the optimal range when heparin was stopped. In most cases, a catheter was inserted via the femoral vein; however, when a patient had a filter in the inferior vena cava, the catheter was inserted through the right jugular vein. A balloon wedge-pressure catheter was inserted into the main pulmonary artery tract and replaced by a long spring guidewire, before a 7- to 9-F coil-construction 80-cm-long sheath was inserted into the main pulmonary artery tract. A 6- to 8-F guide catheter was then inserted through the sheath, and a 0.014-inch guidewire was passed through the target lesion. The target lesions were dilated by a 1.5- to 14.0-mm monorail or over-the-wire balloon catheter. The balloons were inflated by hand through an inflation device for 15 to 30 s until they were fully expanded.

Pulmonary arterial angiography of the lung including target lesions was performed before each session to select and determine the target lesions, but not after the procedure. To check flow appearance and grade of flow after angioplasty, selective angiography of the treated vessels was performed through a catheter engaged in the treated vessel. The balloon size was determined by measurement of vessel diameter by using the ruler to measure the vessel diameter mainly on cine freeze-frame and occasionally on intravascular ultrasound.

The enrolled patients had been treated with appropriate targeted drugs for pulmonary hypertension, such as bosentan, ambrisentan, sildenafil, tadalafil, or beraprost, before the procedure. Epoprostenol, treprostinil, and iloprost were not used in any of the patients.

PTPA GUIDED WITH PRESSURE WIRE: THE DILATION STRATEGY AND THE ENDPOINT OF THE PTPA SESSION. A balloon dilation catheter was inserted through the pressure wire (PrimeWire Prestige, Volcano Corporation, Rancho Cordova, California) when it passed across the target lesion. When it did not, a 0.014-inch guidewire was used with a microcatheter (2.6-F, Finecross, Terumo, Tokyo, Japan) and exchanged to a pressure wire. The PAP proximal and distal to the target lesion and the ratio of the 2 pressures were measured by the pressure wire. Balloon dilation was performed first using a relatively small-sized balloon, and then the balloon size was sequentially increased to obtain larger vascular diameter and greater pulmonary flow in the target lesion.

Since June 2012, the balloon dilation goal in terms of effectiveness was to finish dilation when angiographic pulmonary flow grade (defined in our previous report [3]) achieved grade 3. Since January 2013, after we started using pressure wires, the goal was changed to when the pressure ratio of distal to proximal pressures across the target lesion, as detected by pressure wire, was >0.8. Importantly, however, the dilation was stopped, in terms of avoidance of RPE, when the "Pd" value, the distal mean PAP, indicated by the pressure wire after each dilation reached 35 mm Hg (**Figure 1**) and when the baseline mean PAP was >35 mm Hg. This is because the development of RPE correlates with mean PAP >35 mm Hg before angioplasty, and the median value of mean PAP before angioplasty without any RPE is 33 mm Hg (1,3). Even if the stenosis remains angiographically in the target lesion while the "Pd" values improve to nearly 35 mm Hg, the PTPA procedures should be stopped at this point and shifted to other target lesions. The lesions with residual stenoses should be dilated at the next sessions because the improvement in the proximal PAP cannot be obtained immediately but only several days later (2).

Since June 2012, to prevent RPE, the endpoint for each PTPA session has been determined by PEPSI (sum total change of pulmonary flow grade scores × baseline PVR [Wood units]) scores <35.4 because our previous report (3) demonstrated that the negative predictive value of RPE is 92.3% if the endpoint for each PTPA session is determined by keeping the PEPSI score <35.4.

COMPARISON OF THERAPEUTIC PARAMETERS, RPE, AND VESSEL COMPLICATIONS. Fifty-four patients (initial group) were enrolled during the period from

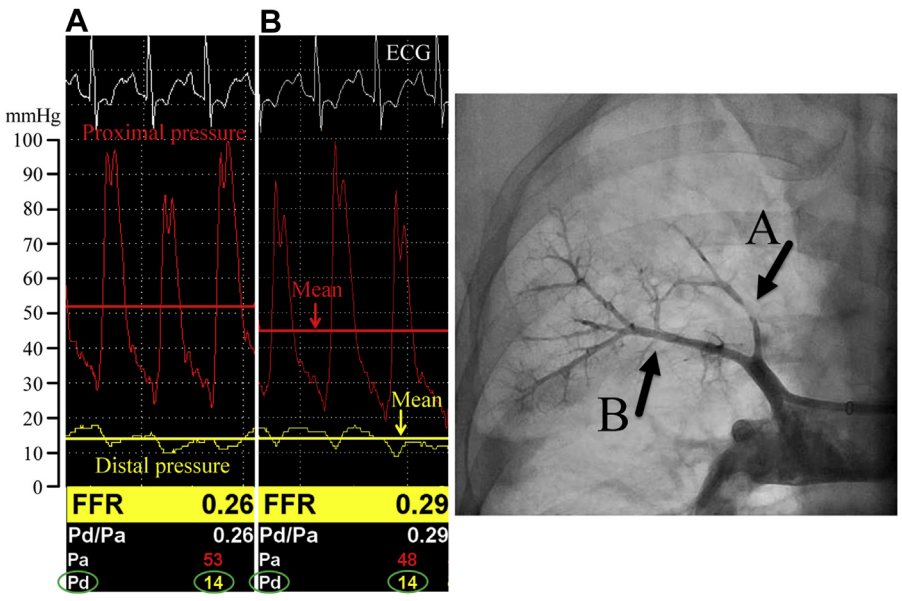

FIGURE 1 Pressure-Wire-Guided PTPA

Panels **A** and **B** show the pressure waveforms obtained by the pressure wire before percutaneous transluminal pulmonary angioplasty (PTPA). The **yellow pressure waveforms** show the distal pressures of the target lesions and the **red** waveforms show the proximal pressures. The digit indicated as "Pd" **(green circles)** is the mean pressure in the distal area across the target lesions. "FFR" value represents the pressure ratios of the distal to proximal pressures across the target lesions. Since June 2012, the balloon dilation endpoints for each lesion in PTPA procedures have been that angiographic pulmonary flow grade achieves grade 3, and since January 2013, that the pressure ratios (indicated as FFR) of distal to proximal pressures across the target lesions achieves >0.8. Importantly, however, the balloon dilations in PTPA procedures were performed so as not to exceed the Pd value of 35 mm Hg. The angiogram shows the selective pulmonary angiography of the right pulmonary A2 segmental branches. **Arrow A** indicates typical stenotic lesion, and the pulmonary flow grade in angiography was 0 (Online Video 1). Therefore, there was severe pressure gradient (pressure ratio indicated by FFR: 0.26) between the proximal and distal sites across this lesion **(A)**. Meanwhile, the lesion indicated by **arrow B** was not viewed as obstructive by the angiography, but pulmonary flow grade was 1, and the pressure wire showed significant pressure gradient (pressure ratio indicated by FFR: 0.29), which was almost the same level as the lesion indicated by **arrow A**, between the proximal and distal sites across the lesion indicated by **arrow B (B)**. Both of the distal pressure waveforms **(yellow waveforms)** in **A** and **B** look like the waveforms of pulmonary arterial wedge pressure due to tight stenosis in the lesions **(arrows A and B)**. The angiography after balloon dilation revealed improved pulmonary flows in both of the lesions (Online Video 2). These suggest that the pressure wire is also useful to identify the sites of the significant lesions that are not so clearly viewed in the angiography. ECG = electrocardiogram; Pa = the mean pressure in the proximal area of the target lesions.

January 2009 to May 2012 (initial period). Then, 12 patients (middle group) were enrolled during the period from June 2012 to December 2012 (middle period). Finally, 37 patients (latest group) were enrolled during the period from January 2013 to December 2013 (latest period). One-hundred forty PTPA sessions were performed during the initial period without the guidance of PEPSI and pressure wire (no-guidance sessions). Then, 65 PTPA sessions were performed during the middle period with guidance of PEPSI (PEPSI-guided sessions), and 145 PTPA sessions during the latest period with guidance of both pressure wire and PEPSI (pressure-wire-and-PEPSI-guided sessions). The hemodynamic parameters, 6MWD, and BNP at baseline just before the first PTPA and at follow-up were compared among these 3 groups. The frequencies of complications of RPE and vascular injuries were compared among the 3 groups.

STATISTICAL ANALYSIS. All data are presented as median (interquartile range). Significant differences were determined using the Mann-Whitney *U* test, Wilcoxon matched-pairs signed rank test, Kruskal-Wallis test, or Dunn multiple comparisons test, as appropriate. Differences in frequencies were analyzed using the chi-square test. Correlation between pulmonary flow grade and the ratio of pressure difference was analyzed using the Spearman rank correlation coefficient. The hemodynamic parameters, 6MWD, and BNP at baseline just before the first procedure and at the time of follow-up after the last PTPA session were compared among the 3 groups by

2-way repeated-measures analysis of variance and Turkey or Sidak multiple comparisons test, as appropriate. Although the number of enrolled patients was 103, follow-up analysis was performed in 83 patients (53, 12, and 18 patients in the initial, middle, and latest groups, respectively), in whom the follow-up examinations had been performed for a total observation period of >30 days. No adjustments were made for multiple sessions within patients in the session-wise analyses. A value of $p < 0.05$ was considered statistically significant.

RESULTS

CLINICAL IMPROVEMENT BY PTPA. The baseline characteristics of the enrolled 103 patients and 3 groups are detailed in Table 1. The numbers of PTPA sessions performed per patient was the lowest in the latest among the 3 groups [median: 3.5 (interquartile range [IQR]: 2.0 to 4.0] sessions vs. 4.0 (IQR: 3.3 to 5.0) sessions vs. 2.0 (IQR: 2.0 to 4.0) sessions; initial group vs. middle group vs. latest group]. The number of treated vessels per patient tended to be lowest in the latest among the 3 groups without statistical significance (median: 12.0 [IQR: 8.0 to 19.3] vessels vs. 15.0 [IQR: 9.3 to 18.0] vessels vs. 9.0 [IQR: 6.5 to 14.0] vessels; initial group vs. middle group vs. latest group). The size of the vessels intervened ranged from 2.0 to 14.0 mm. The percentage of 100% occluded lesions such as complete obstruction and pouch defect was 9.6%, but the vessel sizes of these 100%-occluded lesions were <8.0 mm. The recanalization success rate of the 100%-occluded lesions was 70.4%.

The follow-up analysis, which included 83 patients, showed that the average observation period from the first procedure to the last follow-up was 14.0 (IQR: 7.6 to 21.9) months, and the average number of PTPA sessions per a patient was 3.0 (IQR: 2.0 to 4.0). A comparison of the examinations at baseline with those at follow-up is presented in Figure 2. The right-sided heart catheterization demonstrated a significant improvement in hemodynamic parameters (mean right atrial pressure: 5 [IQR: 3 to 7] mm Hg vs. 3 [IQR: 2 to 5] mm Hg; mean PAP: 41 [IQR: 34 to 47] mm Hg vs. 21 [IQR: 18 to 28] mm Hg; median PVR: 8.7 [IQR: 6.1 to 13.3] Wood units vs. 2.7 [IQR: 2.0 to 4.2] Wood units; and median cardiac index: 2.5 [IQR: 2.1 to 2.9] l/min/m^2 vs. 2.9 [IQR: 2.4 to 3.5] l/min/m^2;

TABLE 1 Baseline Characteristics in Each Group

	Enrolled Patients (N = 103)	Initial Group (n = 54)	Middle Group (n = 12)	Latest Group (n = 37)
Age, yrs	65 (53–72)	64 (55–70)	60 (41–70)	70 (53–76)
Female/male	79/24	41/13	10/2	28/9
NYHA functional class, I/II/III/IV	0/13/74/16	0/4/40/10	0/2/9/1	0/7/24/6
Previous pulmonary endarterectomy	11	6	3	2
Mean RAP, mm Hg	5 (3–8)	5 (3–7)	4 (2–7)	6 (3–8)
Mean PAP, mm Hg	41 (33–48)	43 (37–52)	42 (32–43)	37 (31–48)
PVR, Wood units	8.6 (5.8–12.3)	9.2 (6.9–15.0)	6.5 (5.8–14.5)	7.7 (4.9–11.3)
CI, l/min/m^2	2.5 (2.1–2.8)	2.5 (1.8–2.9)	2.4 (1.9–2.8)	2.5 (2.2–2.8)
PAWP, mm Hg	8 (6–11)	7 (5–10)	9 (5–11)	8 (6–12)
SvO_2, %	66.0 (61.0–71.0)	66.0 (59.7–72.4)	64.7 (61.3–69.7)	66.2 (62.1–69.2)
6MWD, m	348 (258–420) (n = 93)	360 (278–407) (n = 50)	369 (352–457) (n = 11)	327 (250–428) (n = 32)
BNP, pg/ml	94 (42–232)	126 (54–390)	58 (33–181)	61 (39–150)
Total PTPA sessions	350	201	49	100
January 2009 to June 2012	140 (no-guidance sessions)	140	0	0
July 2012 to December 2012	65 (PEPSI-guided sessions)	37 (patients, n = 19)	28	0
January 2013 to December 2013	145 (pressure-wire-and-PEPSI-guided sessions)	24 (patients, n = 13)	21 (patients, n = 8)	100
PTPA session per patient	3.0 (2.0–4.0)	3.5 (2.0–4.0)	4.0 (3.3–5.0)	2.0 (2.0–4.0)*†
Total dilated vessels	1,302	751	168	383
January 2009 to June 2012	525	525	0	0
July 2012 to December 2012	223	135	88	0
January 2013 to December 2013	554	91	80	383
Dilated vessels per patient	11 (7–17)	12 (8–19)	15 (9–18)	9 (7–14)

Values are n or median (interquartile range). *$p < 0.05$ vs. initial group; †$p < 0.01$ vs. middle group.

6MWD = 6-minute walk distance; BNP = B-type natriuretic peptide; CI = cardiac index; NYHA = New York Heart Association; PAP = pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PEPSI = Pulmonary Edema Predictive Scoring Index; PTPA = percutaneous transluminal pulmonary angioplasty; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SvO_2 = mixed venous oxygen saturation.

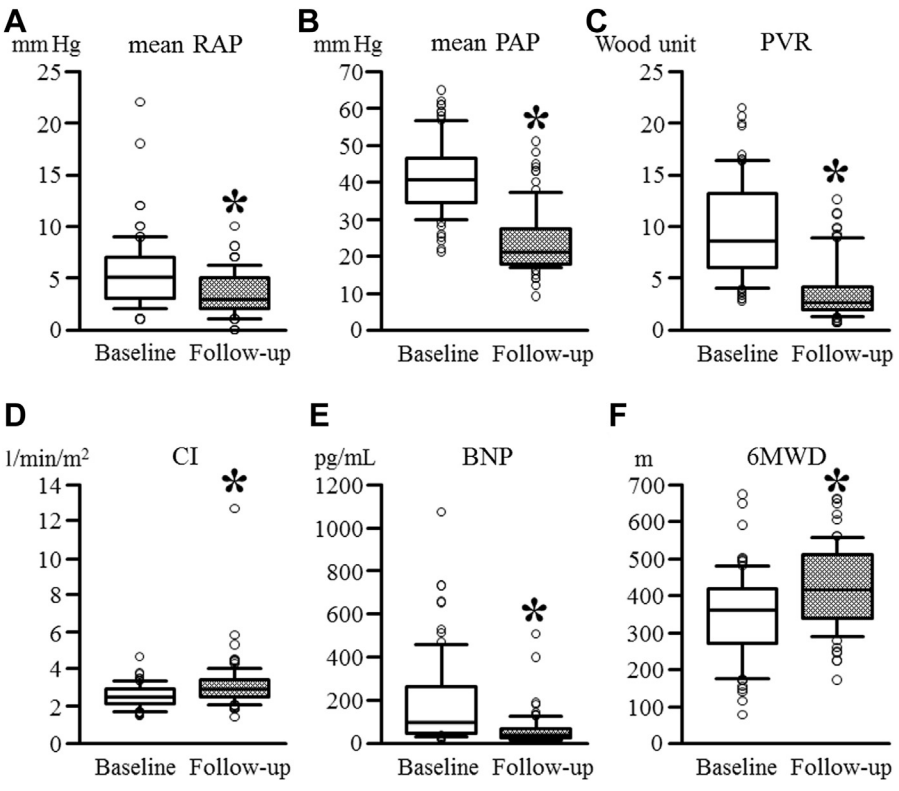

FIGURE 2 Therapeutic Efficacy of PTPA in All the Patients Enrolled

Hemodynamic changes in the mean right atrial pressure (RAP) **(A)**, the mean pulmonary arterial pressure (PAP) **(B)**, the pulmonary vascular resistance (PVR) **(C)**, the cardiac index (CI) **(D)**, and the plasma B-type natriuretic peptide (BNP) **(E)** and 6-min walk distance (6MWD) **(F)** at follow-up after percutaneous transluminal pulmonary angioplasty (PTPA). All hemodynamic parameters, BNP, and 6MWD were significantly improved at follow-up. **Bars** denote medians, **boxes** denote interquartile ranges, **whiskers** denote ranges excluding statistical outliers **(open circles)** (>1.5 box lengths from either the 25th or 75th percentiles). *$p < 0.0001$ versus baseline.

baseline vs. follow-up, $p < 0.0001$, respectively). Plasma BNP was significantly decreased after PTPA (median: 94.5 [IQR: 41.7 to 269.5] pg/ml vs. 33.7 [IQR: 15.8 to 59.2] pg/ml, $p < 0.0001$). The 6MWD was significantly lengthened at the follow-up from 360 (IQR: 281 to 430) m to 420 (IQR: 350 to 510) m ($p < 0.0001$, $n = 69$).

Comparisons among the 3 groups are shown in Figure 3. The average observation periods from the first procedure to the last follow-up were 9.3 (IQR: 6.3 to 14.1) months, 4.8 (IQR: 3.7 to 6.8) months, and 6.4 (IQR: 4.0 to 7.1) months in the initial, middle, and latest groups, respectively. The average number of PTPA sessions per patient was 2.0 (IQR: 2.0 to 4.0), 2.0 (IQR: 2.0 to 3.0), and 2.0 (IQR: 2.0 to 3.3) in the initial, middle, and latest groups, respectively, without statistically significant differences. The degree of improvement in hemodynamics, the levels of BNP, and prolongation of 6MWD were not significantly different among the 3 groups. Additionally, the average reduction rate of mean PAP in patients with baseline mean PAP >40 mm Hg in the latest group was 38.7% (IQR: 27.5% to 48.8%), and that in patients with mean PAP <40 mm Hg was 28.5% (15.4% to 42.2%).

MORTALITY AND VESSEL INJURIES. Among 103 patients enrolled, 1 patient died in the initial group. The patient had severe right heart failure before PTPA and developed pulmonary hemorrhage as a complication because of wire perforation during the procedure. Although the perforation was completely sealed, right heart failure was exacerbated and caused the patient to die 2 days after the session. Therefore, the mortality associated with the PTPA procedure was 0.97%.

Table 2 shows the baseline characteristics of session-based subgroups divided by the methods of guidance. Among the total of 350 sessions, a dissection of the targeted pulmonary artery just

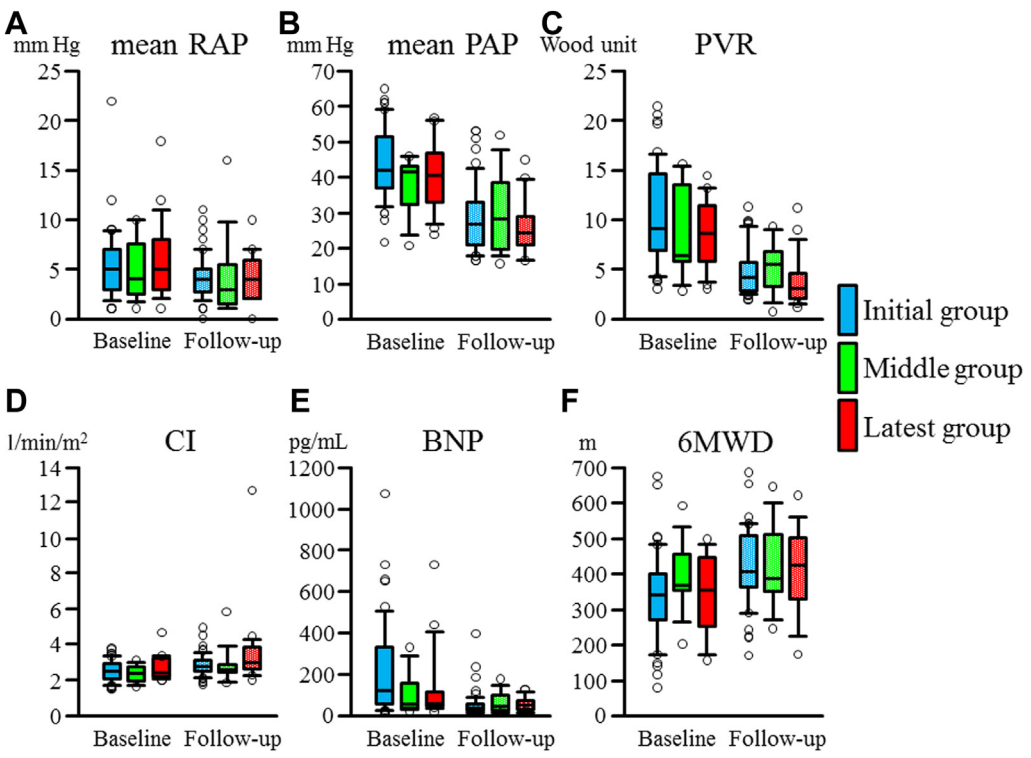

FIGURE 3 **A Comparison of Therapeutic Efficacy Among the 3 Groups**

Hemodynamic changes in mean RAP **(A)**, mean PAP **(B)**, PVR **(C)**, and CI **(D)** and plasma BNP **(E)** and 6MWD **(F)** at the follow-up after PTPA in the 3 groups (initial, middle, and latest). **Bars** denote medians, **boxes** denote interquartile ranges, **whiskers** denote ranges excluding statistical outliers **(open circles)** (>1.5 box lengths from either the 25th or 75th percentiles). Abbreviations as in Figures 1 and 2.

after balloon dilation, without extravascular leaks, occurred in 7 sessions (5 in the no-guidance sessions and 2 in the PEPSI-guided sessions), but the hemodynamics did not significantly change by dissections, and pulmonary angiography after 1 week revealed spontaneous disappearance of the dissections in all the cases. Extravascular leaks occurred just after the balloon dilation in 28 sessions (15 in the no-guidance sessions, 3 in the PEPSI-guided sessions, and 10 in the pressure-wire-and-PEPSI-guided sessions), in which they were stopped by prolonged low-pressure dilation of the balloon in 15 sessions (6 in the no-guidance sessions including the 1 deceased patient, 2 in the PEPSI-guided sessions, and 7 in the pressure-wire-and-PEPSI-guided sessions), by insertion of the covered stent in 1 session without the guide, by coiling in 1 session without the guide, and spontaneously in 11 sessions (7 sessions without guidance, 1 in the PEPSI-guided sessions, and 3 in the pressure-wire-and-PEPSI-guided sessions). In summary, the total rate of angiographic complications was 14.3%, 7.7%, and 6.9% in the no-guidance, PEPSI-guide, and both pressure-wire-and-PEPSI-guide sessions, respectively.

FREQUENCY OF REPERFUSION PULMONARY EDEMA. Table 3 shows the distributions of graded RPE. RPE of grade 1 or 2, which means no clinically critical RPE, was statistically higher in the PEPSI-guided and

TABLE 2 **Baseline Characteristics in Each Subgroup**

	No-Guidance Sessions (n = 140)	PEPSI-Guided Sessions (n = 65)	Pressure-Wire-and-PEPSI-Guided Sessions (n = 145)
Period	1/2009–6/2012	7/2012–12/2012	1/2013–12/2013
Mean RAP before session, mm Hg	4 (3–6)	4 (2–6)	5 (3–7)
Mean PAP before session, mm Hg	38 (30–45)	29 (23–36)*	32 (26–38)*
PVR before session, Wood units	7.2 (4.6–10.9)	4.8 (3.0–6.5)*	5.3 (3.4–7.7)*
CI before session, l/min/m^2	2.5 (2.2–3.1)	2.6 (2.2–3.1)	2.7 (2.4–3.2)
PAWP before session, mm Hg	8 (6–9)	8 (6–10)	9 (6–12)*
SvO_2 before session, %	67.6 (63.2–72.7)	68.2 (62.6–72.5)	68.2 (63.9–72.2)
Dilated vessels	4 (2–5)	3 (2–4)	4 (2–5)

Values are median (interquartile range). *p < 0.01 vs. no-guidance sessions.
Abbreviations are defined in Table 1.

TABLE 3 Classification and Frequency of Reperfusion Pulmonary Edema

Grade	Definition of Graded Reperfusion Pulmonary Edema	Total PTPA Sessions	No-Guided Sessions	PEPSI-Guided Sessions	Pressure-Wire-and-PEPSI-Guided Sessions
1	No significant recognition of reperfusion pulmonary edema on chest x-ray	271 (77.4)	87 (62.1)	59 (90.8)	125 (86.2)
2	Mild or small reperfusion pulmonary edema on chest x-ray, but spontaneous improvement with only a small increase in inhalation of oxygen concentration for a few days	58 (16.6)	35 (25.0)	5 (7.7)	18 (12.4)
3	Moderate reperfusion pulmonary edema on chest x-ray that needed elevated concentration of oxygen administered via oxygen mask to maintain arterial saturation at optimal level	12 (8.6)	9 (6.4)	1 (1.5)	2 (1.4)
4	Moderate to severe reperfusion pulmonary edema on chest x-ray requiring noninvasive positive pressure ventilation with high-concentration oxygen inhalation	7 (2.0)	7 (5.0)	0 (0)	0 (0)
5	Extremely severe reperfusion pulmonary edema on chest x-ray requiring artificial ventilation	2 (0.6)	2 (1.4)	0 (0)	0 (0)

Values are n (%).
Abbreviations as in Table 1.

pressure-wire-and-PEPSI-guided sessions (98.5% and 98.6%, respectively). Meanwhile, RPE of grade 4 or higher, which means clinically critical RPE requiring noninvasive positive pressure ventilation or artificial respiration, in the no-guidance sessions, PEPSI-guided sessions, and pressure-wire-and-PEPSI-guided sessions occurred in 9 (6.4%), 0 (0%), and 0 (0%) sessions, respectively, with statistically significant differences.

FLUOROSCOPY TIME AND X-RAY EXPOSURE. Median fluoroscopy time in the no-guidance, PEPSI-guided, and pressure-wire-and-PEPSI-guided sessions were 74.1 (IQR: 57.9 to 89.9) min, 79.8 (IQR: 63.3 to 94.3) min, and 74.8 (IQR: 59.0 to 91.5) min, respectively. There was no significant difference in fluoroscopy time among the 3 session-based subgroups. Meanwhile, median x-ray exposure in the no-guidance, PEPSI-guided, and pressure-wire-and-PEPSI-guided sessions were 1,531 (IQR: 765 to 2,621) mGy, 1,102 (IQR: 565 to 1,890) mGy, and 953 (IQR: 527 to 1,784) mGy, respectively. X-ray exposure in PEPSI-guided and pressure-wire-and-PEPSI-guided sessions were significantly lower than in the no-guidance sessions (no-guidance vs. PEPSI-guided sessions, $p < 0.05$; no-guided vs. pressure-wire-and-PEPSI-guided sessions, $p < 0.001$). Radiation-induced injury (of any kind) did not occur in any session-based subgroup.

CORRELATION BETWEEN PULMONARY FLOW GRADE SCORES AND THE PRESSURE RATIOS ACROSS THE LESIONS. In the pressure-wire-and-PEPSI-guided sessions, we analyzed the correlation between pulmonary flow grade scores and the pressure ratios across the lesions detected by the pressure wire. We performed 891 measurements of the pressure ratios in 493 of 554 target vessels with pulmonary flow grades 0 to 3 in 145 pressure-wire-and-PEPSI-guided sessions. Figure 4 shows the correlation between the pulmonary flow grade score and the pressure ratios, demonstrating strong correlation ($R = 0.90$, $p < 0.0001$). Furthermore, the distributions of pressure ratios in each pulmonary flow grade were 0.20 (IQR: 0.14 to 0.30; minimum: 0.03, maximum: 0.63), 0.30 (IQR: 0.24 to 0.38; minimum: 0.06, maximum: 0.78), 0.60 (IQR: 0.50 to 0.70; minimum: 0.30, maximum: 0.88), and 0.90 (IQR: 0.81 to 1.00; minimum: 0.54, maximum: 1.00) in pulmonary flow grades 0, 1, 2, and 3, respectively.

DISCUSSION

In the present study, we demonstrated the following: 1) the PTPA technique using pressure wire and PEPSI attained more efficient clinical results, meaning that the same results were obtained by dilating fewer lesions and performing fewer PTPA sessions because the pressure wire can detect pressure gradients across the lesions objectively and quantitatively, leading to a reduction of insufficient dilation left; and 2) the guided technique with both the pressure wire and PEPSI contributed to the establishment of PTPA as the low-risk, promising strategy for CTEPH.

On the basis of the report of Feinstein et al. (1) and our initial PTPA experience, eliminating RPE has been an essential component of developing a safe PTPA approach. In fact, Feinstein et al. (1) reported that about 60% of the treated patients developed RPE after the procedures. RPE has been the most important complication in pulmonary angioplasty, which

sometimes leads to grave morbidity and mortality. With PTPA, most of the lesions cannot be treated at once because when each lesion is dilated, it is exposed to high PAP. In contrast, with pulmonary endarterectomy, the majority of the lesions are removed in 1 procedure. This difference may explain why the incidence of reperfusion lung injury has been higher with PTPA than with pulmonary endarterectomy in the past. Importantly, these findings provided us with the inspiration that demonstrate that it is crucial to conquer RPE to control and suppress the pressure levels distal to the target lesions to certain levels after dilation during the PTPA procedure.

The pressure wire technique has been used in percutaneous coronary intervention with great success in terms of determining the lesions and confirming results (12). Thus, this technique was used in PTPA procedures in our study. Balloon dilation of the target lesions was stopped when pressure levels distal to the target lesions reached nearly 35 mm Hg if baseline mean PAP was more than this level. The criteria of 35 mm Hg was adopted because development of RPE correlates with mean PAP >35 mm Hg before angioplasty, and the median value of mean PAP before angioplasty without any RPE was 33 mm Hg (1,3). Neither the PEPSI-guided nor pressure-wire-and-PEPSI-guided sessions induced any clinically critical RPE without the use of a noninvasive positive pressure ventilator or mechanical ventilator. PEPSI is a promising predictor to avoid significant RPE (3). However, PEPSI is not an objective method, and a combination of the PEPSI score determined subjectively and the pressure-wire technique determined objectively can avoid significant RPE with higher probability. Additionally, the total rate of angiographic complications was lower in the PEPSI-guided and pressure-wire-and-PEPSI-guided sessions than in the no-guidance sessions. One of the important benefits of the pressure-wire technique is that the pressure levels distal to the target lesions can be controlled; another is that overdilation of the target vessels by balloon catheters can also be avoided. This might contribute to the lowest rate of angiographic complications in the pressure-wire-and-PEPSI-guided sessions. These findings suggest that the pressure-wire technique may have advantages in reducing the risk of the vessel injuries during the procedure as well as the risk of significant RPE afterward.

In our PTPA procedures, the target lesions located in segmental, subsegmental, and more distal pulmonary arteries and the size of the vessels intervened was 2.0 to 14.0 mm (the vessel sizes of 100%-occluded lesions were <8.0 mm). The degrees of hemodynamic improvement were not significantly different among the initial, middle, and latest groups. Furthermore, the number of performed PTPAs and the number of treated target lesions were lowest in the latest group compared with those in the other 2 groups. These findings suggest that the pressure-wire technique attained the better hemodynamic improvement in fewer target lesions treated and fewer PTPAs performed. In the pressure-wire-and-PEPSI-guided sessions, the targeted endpoint of balloon dilation for each lesion was to achieve >0.8 of the pressure ratio detected by the pressure wire. Pulmonary flow grade scores and the pressure ratios were significantly correlated in this study. Importantly, however, the pressure ratios in each pulmonary flow grade showed wide distributions. For example, the median pressure ratios in pulmonary flow grade 3 were 0.90 (IQR: 0.81 to 1.00; minimum: 0.54, maximum 1.00) in this study. These findings imply that if pulmonary flow grade 3 is obtained after dilation of the target lesions by balloon catheters, there are some cases with pulmonary flow grade 3 in which pressure ratios were <0.8, meaning that significant stenosis remained in these lesions.

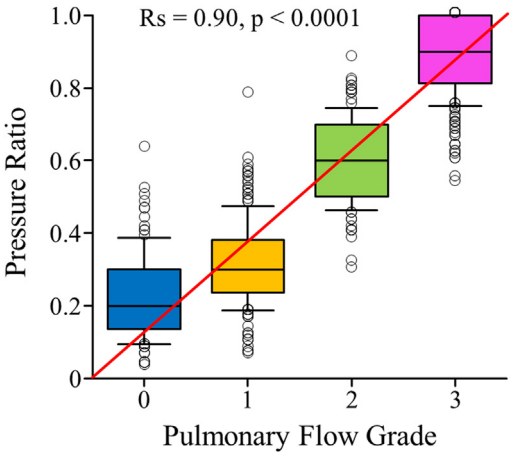

FIGURE 4 Correlation Between Pulmonary Flow Grade Score and the Ratio of Proximal and Distal Pressures of the Target Lesions

Pulmonary flow grade scores were strongly correlated with the pressure ratios. The median distributions of the pressure ratios in each pulmonary flow grade were 0.20 (IQR: 0.14 to 0.30; minimum: 0.03, maximum: 0.63), 0.30 (IQR: 0.24 to 0.38; minimum: 0.06, maximum: 0.78), 0.60 (IQR: 0.50 to 0.70; minimum: 0.30, maximum: 0.88), and 0.90 (IQR: 0.81 to 1.00; minimum: 0.54, maximum: 1.00) in pulmonary flow grades 0, 1, 2, and 3, respectively. **Bars** denote medians, **boxes** denote IQRs, **whiskers** denote ranges excluding statistical outliers **(open circles)** (>1.5 box lengths from either the 25th or 75th percentiles). IQR = interquartile range.

Pressure-wire-guided detection of the pressure ratios across the target lesions and the targeted endpoint to achieve >0.8 of the pressure ratios might reduce the number of insufficiently dilated lesions left with pulmonary flow grade 3. It also shows why PTPA yields more efficient results in the pressure-wire-and-PEPSI-guided PTPA sessions.

Furthermore, the pressure wire was useful to identify abnormal lesions that were not so clearly viewed by angiography. In **Figure 1**, the lesion indicated by arrow A was clearly viewed on angiogram, and pulmonary flow grade was 0 before PTPA. The lesion indicated by arrow B was not so clearly viewed by angiography, but pulmonary flow grade was 1, and the pressure wire was useful in identifying the significant stenotic lesion in this case. Online Video 1 shows angiography of these lesions before PTPA, and Online Video 2 shows angiography after PTPA, demonstrating the improved angiographic flow of these lesions. These findings demonstrate that the pressure wire was useful for identifying the significant lesions precisely and to avoid overlooking the lesions that were not so clearly observed by angiography.

STUDY LIMITATIONS. This was a retrospective case-control study. The number of patients enrolled was not large, and the observation period and number of patients distributed among the 3 groups were different. Furthermore, because the possible impact of a learning curve cannot be ruled out, there is a possibility that the low rate of complications in the latest group may be related not only to pressure-wire-guidance but also to greater operator experience. In addition, because the inclusion criteria were changed during the study, there is a possibility that selection process affected the results. To demonstrate usefulness and efficiency of the pressure-wire-and-PEPSI-guided PTPA procedure, a large-scaled collaborative prospective study in the near future is strongly desired.

CONCLUSIONS

There were no clinically critical RPE and vessel injuries when PTPA was performed using the pressure-wire-and-PEPSI-guided technique. Pressure wire was efficient in obtaining good clinical results. Therefore, the findings in this study indicate that pressure-wire-and-PEPSI-guided PTPA is effective in CTEPH, improves procedural success rates, and reduces the risk of the procedure.

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KEY WORDS chronic thromboembolic pulmonary hypertension, percutaneous transluminal pulmonary angioplasty, pressure wire, Pulmonary Edema Predictive Scoring Index, reperfusion pulmonary edema

APPENDIX For accompanying videos, please see the online version of this article.